Complexities of Inheritance

Introduction

Some features of genetics can make "simple" inheritance patterns harder to figure out. Not everything obeys simple Mendelian inheritance, where there's just one good allele and one bad allele. In this lesson we'll highlight some of the hot topics and cover vocabulary that illustrates how genetics is not deterministic—that phenotype sometimes is reliably determined by genotype but can also vary based on more than just the genetic code.

Anticipation

Certain diseases possess a quality known as **anticipation** whereby **the most recent generation develops symptoms earlier than previous generations**. The longer the gene is in the gene pool, the more generations it's replicated and passed down, the sooner and more severe the symptoms become. This phenomenon is seen in **myotonic dystrophy**, **fragile X**, and **Huntington's disease**.

It's caused by **trinucleotide repeat expansion**. Some trinucleotide repeats in our DNA work just fine. But with others, such as **CAG** in Huntington's, the **DNA polymerase duplicates CAG more times than the template says to**. This means that in generation 1 there are so many CAGs, and in generation 2 there are more CAGs, and in generation 3 there are even more CAGs. This increase in number (expansion) of the trinucleotide (C, A, and G are three, tri-) causes more severe disease with an earlier onset.

What makes a pedigree difficult to assess is **delayed age of onset**. Since pedigrees are phenotypic, if an individual doesn't develop symptoms until later in life, his phenotype may be erroneously counted as "negative" simply because it hasn't yet had time to set in. Dementia, for example, is not only multifactorial but also only appears after many decades of life.

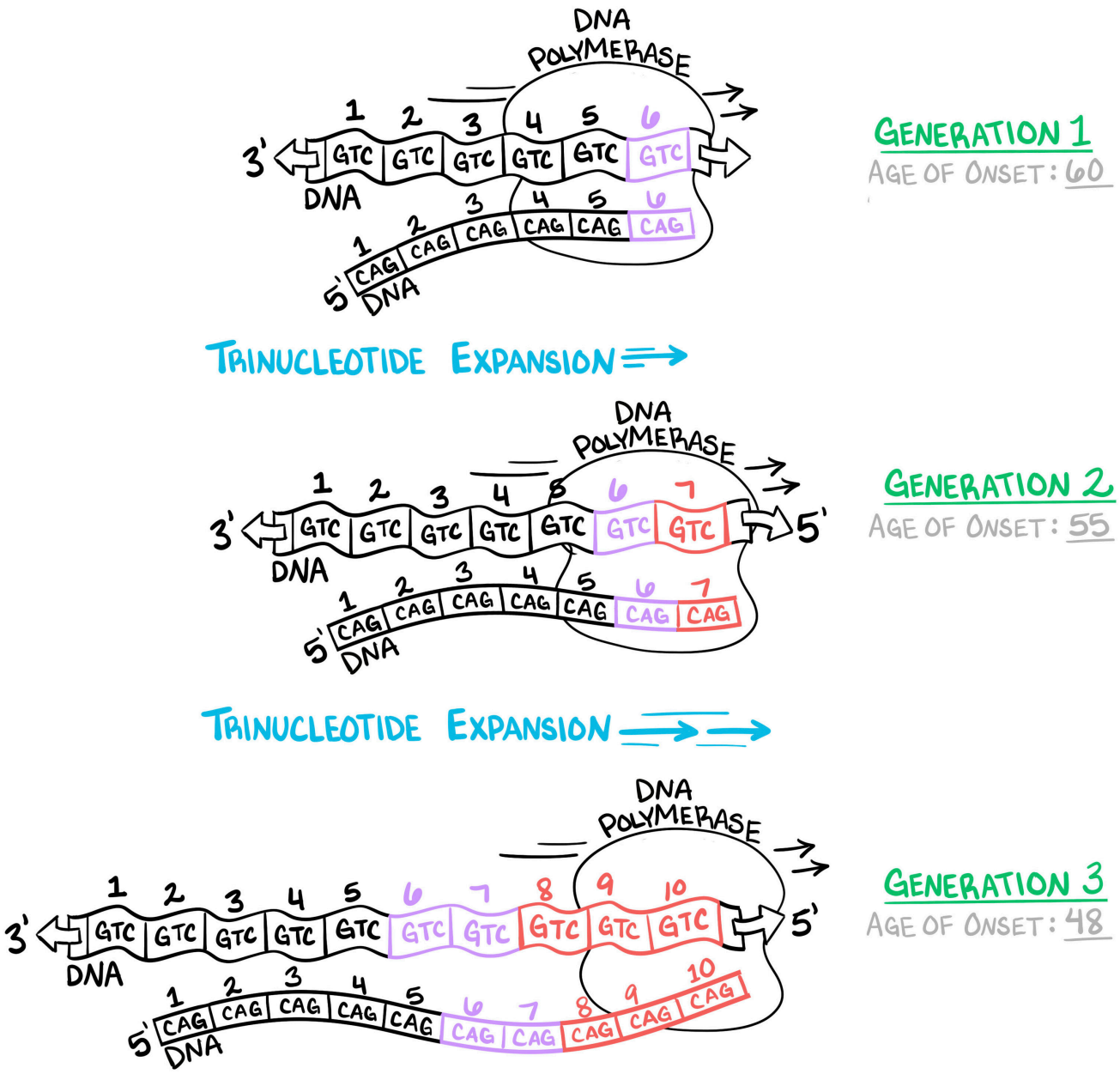

Figure 3.1: Anticipation, Trinucleotide Repeat Expansion
In Huntington's, the CAG trinucleotide repeat not only gains repeats (expansion), it also causes the disease to be expressed earlier in life (anticipation).

Imprinting

Prader-Willi and Angelman syndromes, the process of methylation to turn off genes, and the deletion of the corresponding chromosomes, are discussed in Biochemistry: DNA to Protein. Females imprint (methylate, turn off) the Prader-Willi genes and leave active the Angelman. Males imprint (methylate, turn off) the Angelman gene and leave on the Prader-Willi genes. If there's a **deletion of dad's DNA,** the active genes (Prader-Willi) are lost, and because mom's copy was methylated (turned off), the baby gets Prader-Willi. Even though mom's DNA for the gene is there, it's imprinted off. If there's a **deletion of mom's DNA**, only dad's genes are left, and his genes methylated (turned off) Angelman, so baby

gets Angelman syndrome. **Imprinting** is normal and healthy—two active copies of some genes causes problems. Both Angelman and Prader-Willi occur only when there's imprinting (always) **and a deletion**.

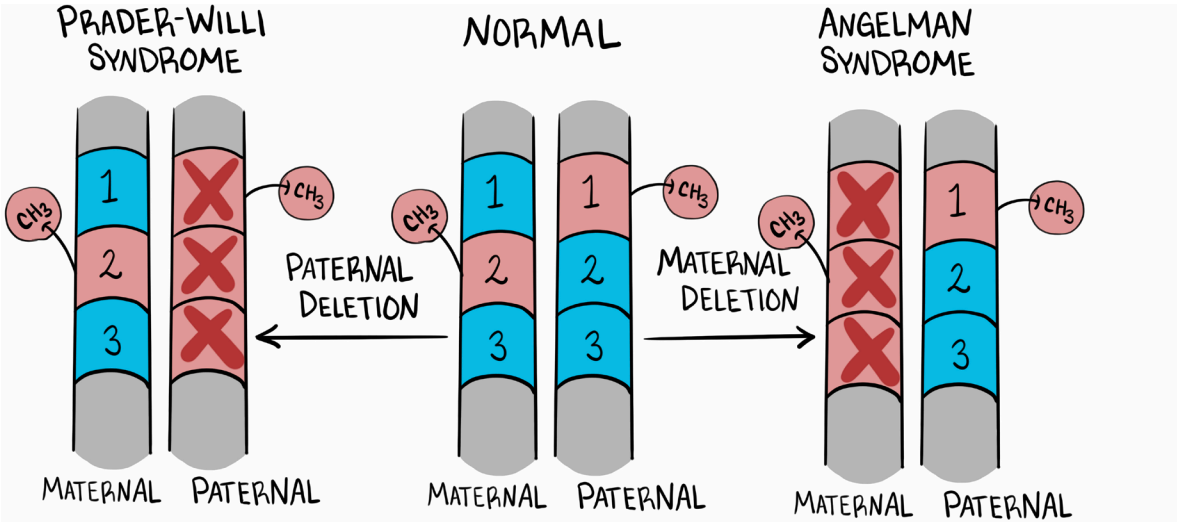

Figure 3.2: Imprinting and Methylation
Maternal and paternal genes are methylated—inactivated—differently. Normally this produces an offspring with the right number of genes. But should a deletion of one sex's copy occur, the other sex's methylated copy means that there isn't enough gene to make sufficient protein.

Variable Expression vs. Incomplete Penetrance

Students have trouble with these terms because they're taught at the same time and their English implications are vaguely similar.

Incomplete penetrance means that a genotype doesn't guarantee expression of a disease. It's best illustrated by the breast cancer gene mutation BRCA-1. If a woman has the BRCA-1 mutation, there's an 80% chance that she'll eventually develop breast cancer. That 80% is based on extensive epidemiological studies. Thus, the penetrance of BRCA-1 is 80%.

Incomplete penetrance says that when a genotype is possessed, the disease may not express itself.

Variable expression means that just because a phenotype is expressed (the genotype is expressed), it may be different than another person with the same genotype. Simply put, we might say, "**disease presents differently in different people**." That isn't profound. Mary's breast cancer is not Beth's breast cancer. My hypertension is not your hypertension. They're treated differently, the symptoms are different, and individuals are in fact individuals. For genetic diseases, there's a reproducibility that makes them comfortable diseases to memorize. However, as in most things, the genetic code alone doesn't determine what the patient experiences. Trisomy 21 has varying degrees of intellectual disability; some sickle-cell patients have crises monthly, while others may go a year without seeing a hospital. The list goes on and on.

Variable expression says that when a genetic disease is expressed, its expression is different person to person.

Illustrating the terms further, with an 80% penetrance of the BRCA-1 mutation causing breast cancer, there's an 80% chance that a woman with BRCA-1 will get breast cancer in her lifetime (**incomplete penetrance**). This woman who gets breast cancer from BRCA-1 has a different disease presentation, a different cancer than that woman with the same BRCA-1 mutation (**variable expression**).

Why this matters: **incomplete penetrance can confound a pedigree**. As one analyzes a family tree it becomes clear that there is an autosomal dominant disease—males and females, males to males, every

generation. Yet somehow, one particular person gets "skipped." These two pedigrees show the confusion. Both pedigree trees are of the same family. The one on the left shows the phenotype pedigree—the circled white square is able to pass down the disease but is not affected himself. The one on the right shows the genotype pedigree. The circled black square has the genotype to express disease but didn't. That—having-the-genotype-but-not-phenotype—is incomplete penetrance.

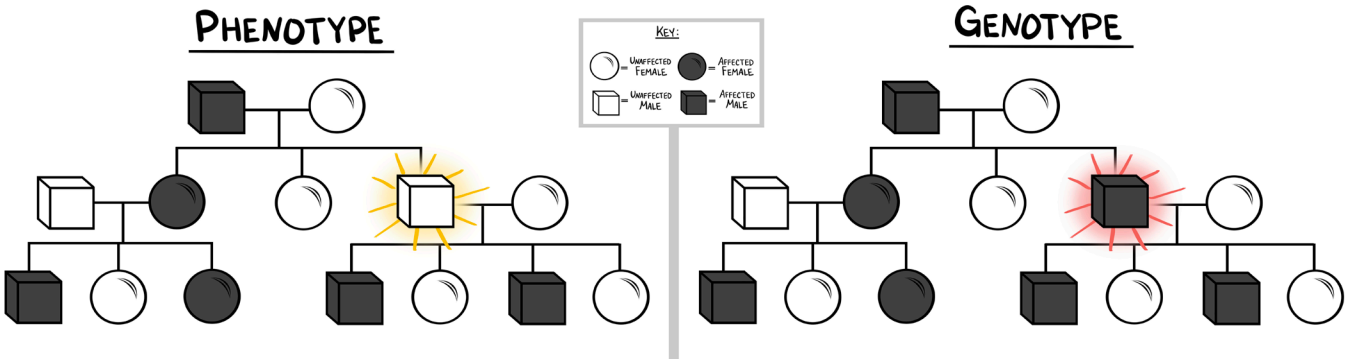

Figure 3.3: Incomplete Penetrance
A man may show no sign of the genetic disorder phenotypically (yellow highlight), yet still possess the genes to affect half his children (red highlight). More importantly, an affected male not passing on to his son but to his daughter appears to be X-linked dominant, yet phenotypically, the third generation shows males affected by an unaffected mating. The genotype pedigree shows the true autosomal dominant pattern.

Pleiotropy

This term means "if you have a mutation, it can cause more than one symptom." The magic in this is that the symptoms are seemingly unrelated phenotypic traits. It's a term of history. We look at a sick child with a funny smell, intellectual disability and pale skin (the odor, the brain, the skin being "unrelated" on a review of systems), and find that it's instead just one genetic disorder (phenylketonuria). In medicine, our job is to take the "unrelated" symptoms and combine them into a syndrome that matches an illness script. We're supposed to recognize that a funny smell + intellectual disability + pale skin + in a child = PKU.

Pleiotropy basically says that **genotype changes cause phenotype syndromes** (syndromes being a collection of symptoms).

Marfan syndrome is also always used to demonstrate pleiotropy. It's caused by a mutation in the **fibrillin gene**. Fibrillin is used in connective tissue, collagen, and joints. So the mutation of fibrillin causes a syndrome throughout the body. Wherever fibrillin is supposed to do its thing, it does its thing wrong. The results of the syndrome are **thin**, **elongated limbs and fingers**, **hypermobile joints**, and most importantly, **aortic aneurysms** or mitral valve prolapse.

Locus Heterogeneity

To demonstrate the complexity of proteins, this term is used when there's **one common** phenotype and **one common disease presentation,** but which can be caused by **mutations in different places.** An example is in osteogenesis imperfecta, where small trauma causes massive fractures in a neonate. It's a super-specific syndrome. But that one disease state is caused by **mutation of either chromosome 7 or chromosome 17.**

This example is explained by the fact that collagen isn't made on one protein. All connective-tissue collagen is more complex than that, and pieces of the final product of collagen are made from chromosome 7 and chromosome 17. It's as if "collagen" is stored in the genetic code across multiple chromosomes.

New Mutation

It's possible that the gametes develop a mutation in meiosis. It's possible that the fertilized egg develops a mutation very early on in development. If that's the case, mom and dad have no genetic recollection of the mutation or the disease. But the child now has that bad gene in every single cell. Somatic mutations happen all the time—we have DNA repair mechanisms specifically to prevent them from occurring, and fixing them when they do.

But they still happen. The only way the test can ask for identification of a new mutation is if a pedigree has no history at all of any kind of a disease, and suddenly it appears. Now with genetic testing, we're able to assess for the gene mutations in mom and dad, and if not found, assume that the child had a random mutation (though failure of paternity is far more common than new mutation).

Genetic Mosaicism

A human comes from one fertilized cell. Every cell has all of the genetic material from that one cell. Hence, every single cell is a clone of another cell in the body. But what if in the earliest stages of development, when we were only 4 cells big, there was a mutation in one of those cells? In three of the four cells, A is A. But in one cell, A is G. One-fourth of our cells would have that mutation from A to G. One-fourth of our cells would express the mutation, while three-fourths wouldn't; they'd be normal.

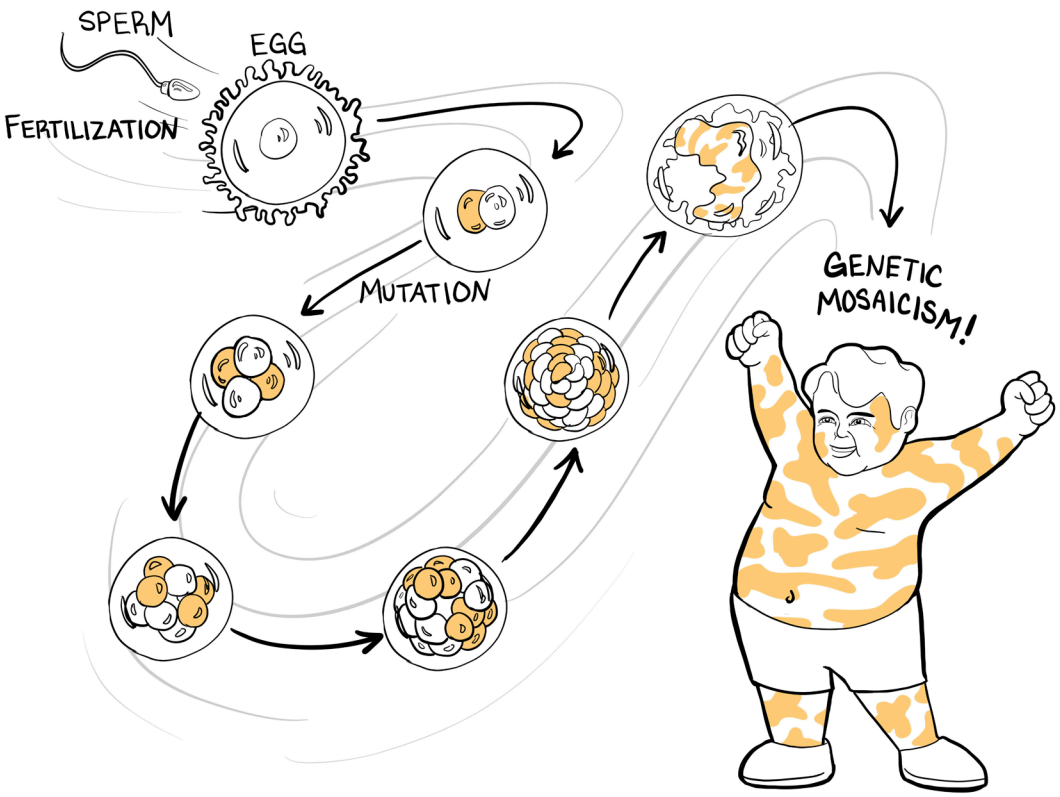

Figure 3.4: Genetic Mosaicism
An early mutation in a zygotic cell proliferates just as much as the non-mutated cell lines. The earlier in the zygote's maturation, the more evenly distributed the mutation can be. A somatic mutation in a fully formed adult would have almost no effect. A mutation in the second cell after the first division would cause 50% of the mutation everywhere in the body.

Being a "mosaic" means we could have 20 cells next to each other, all in the same organism, and yet not all have the same genetic code. This is a consequence of a "new mutation" and must occur after fertilization.